CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208215Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review	
NDA	208215
Submission Type	505(b)(1)
Applicant	Gilead Sciences, Inc.
Submission Date	04/07/2015
Generic Name	Emtricitabine (FTC)/Tenofovir alafenamide (TAF)
Trade Name	DESCOVEY
Dosage Form (Strength)	[redacted] (b) (4) FDC Tablet (FTC 200 mg / TAF 25 mg)
Proposed Indication	Treatment of HIV-1 infection in adults and pediatrics patients 12 years of age and older.
CDTL	Islam R. Younis, Ph.D.
Recommendation	Approval

1. Introduction

Emtricitabine (FTC) is a nucleoside reverse transcriptase inhibitor approved (initial approval in 2003) for treatment of HIV-1 in combination with other antiretroviral (ARV) agents in adults and pediatrics 0 month through 17 years of age. Tenofovir alafenamide (TAF) is a prodrug of the nucleotide reverse transcriptase inhibitor tenofovir (TFV) approved (initial approval in 2015) as part of the fixed dose combination GENVOYA® (Elvitegravir (EVG)/Cobicistat (COBI)/FTC (200 mg)/TAF (10 mg)). GENVOYA® is indicated for treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older who have no antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically-suppressed (HIV-1 RNA less than 50 copies per mL).

2. Background

The Applicant developed a fixed dose combination (FDC) tablet containing FTC and TAF [redacted] (b) (4) FTC/TAF 200/25 mg. The proposed indication is to use the FDC in combination with other ARV agents, for treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older.

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FTC/TAF is not a complete regimen for treatment of HIV-1 infection. It must be combined with other ARV agents to form a complete regimen. The selection of the ARV agent has an impact on the dosage of TAF. For example, protease inhibitors (PIs) are generally administered with a CYP3A4 inhibitor such as ritonavir (RTV) or COBI to increase exposure of the PIs. These CYP3A4 inhibitors also increase TAF exposure by 2.65 fold. The optimal dose of TAF was determined to be 25 mg based on antiviral activity monotherapy trial. Therefore, (b) (4) FTC/TAF 200/25 mg FDC was developed for use with ARV agents in regimens that do not contain a CYP3A4 inhibitor (b) (4)

The Applicant is seeking approval of the current application based on the results of two relative bioavailability studies:

(b) (4)

2. Study GS-US-311-1473: FTC and TAF exposures were compared following the administration of FTC/TAF 200/25 mg FDC vs. the administration of EVG/COBI/FTC/TAF FDC.

A clinical trial to evaluate the efficacy and safety of FTC/TAF FDC was not required because the efficacy and safety of FTC and TAF was established previously in:

1. Trials of FTC + TAF with EVG + COBI in HIV-1 infected adults as initial therapy in those with no ARV treatment history (n=866) and to replace a stable ARV regimen in those who were virologically-suppressed for at least 6 months with no known resistance substitutions (n=799). At Week 48, 92% and 96% of patients in the two populations, respectively, had HIV-1 RNA less than 50 copies per mL.
2. A trial of FTC + TAF with EVG + COBI in 23 treatment-naïve HIV-1 infected pediatric patients aged 12 to less than 18 years old and greater than 35 kg, the virologic response rate (i.e., HIV-1 RNA less than 50 copies per mL) was 91% at 24 weeks.
3. A trial of FTC+TAF with EVG + COBI in HIV-1 infected patients with creatinine clearance greater than 30 mL minute (n= 248). Of the 248 patients, 6 were treatment naïve and 242 were virologically suppressed (HIV-1 RNA less than 50 copies per mL for at least 6 months before switching to FTC + TAF with EVG + COBI). At Week 24, 83% (5/6) of treatment naïve and 95% (236/248) of virologically suppressed subjects had HIV-1 RNA less than 50 copies per mL.

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3. Product Quality

The NDA is recommended for approval from product quality perspective. Satisfactory information and responses have been submitted to support the quality of the drug substances and drug product. All manufacturing facilities have been determined to be in acceptable status. Please refer to the Office of Pharmaceutical Quality review dated 02/23/2016 for full details.

Drug Substance: The manufacturing and quality attributes of the two active pharmaceutical ingredient components (FTC and TAF) of the FDC are acceptable because they were previously reviewed and approved by FDA in the cross-referenced NDAs.

Drug Product: The drug product is a monolithic tablet with two drug substances, and is produced using conventional pharmaceutical processes. The specification includes tests for appearance, identity, water, assay, degradants, uniformity, dissolution, and microbial limits. The specification is largely conventional for an immediate release solid oral dosage form and a satisfactory justification is provided. The limit for [redacted] (b) (4) from no more than (NMT) [redacted] (b) (4) % to NMT [redacted] (b) (4) % to reduce the risk of TAF-associated degradants exceeding their acceptance criteria on storage. The degradants are toxicologically qualified at the proposed limits. The analytical methods are described in reasonable detail and have been validated and shown to be reasonably robust. Satisfactory batch analyses are provided for 5 batches of each strength.

Stability data support a 24 month expiration dating period with the storage statement: "Store below 30°C".

Dissolution: The proposed dissolution methods for FTC and TAF and the revised similar acceptance criteria (Q= [redacted] (b) (4) % at 30 minutes) for the two dosage strength are acceptable.

Packaging: The tablets are packaged in HDPE bottles containing 30 tablets, a silica gel desiccant, polyester coil, and closed with a child-resistant closure.

4. Nonclinical Pharmacology/Toxicology

The NDA is recommended for approval from pharmacology and toxicology perspective. Please refer to the pharmacology and toxicology reviews dated 12/02/2015 and 12/03/2015 for full details.

All nonclinical information for the current NDA is cross-referenced to the original NDAs and INDs and no additional nonclinical toxicology information is included in the submission package. The information was deemed sufficient during the review of the referenced NDAs. The

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target organs of toxicity are different for the two drugs; therefore, administration of FTC and TAF in combination is unlikely to exacerbate known toxicities of the two individual agents. The impurities and degradation products present in FTC and TAF and in FTC/TAF tablets have been qualified through toxicology studies.

5. Clinical Pharmacology and Biopharmaceutics

The NDA is recommended for approval from clinical pharmacology and biopharmaceutics perspective. Please refer to the clinical pharmacology review dated 12/07/2015 and product quality review (contains biopharmaceutics review) dated 02/23/2016 for full details.

Two pivotal relative bioavailability studies constitute the basis of approval for this application:

(b) (4)

2. Study GS-US-311-1473 is a randomized, open-label, single-dose, two-way cross-over study which compared FTC and TAF exposures following the administration of FTC/TAF 200/25 mg FDC and following the administration of EVG/COBI/FTC/TAF FDC under fed conditions.

As shown in Figure 1, similar exposures of FTC and TAF from (b) (4) FTC/TAF FDC dosage (b) (4) and the reference (EVG/COBI/FTC/TAF FDC) were demonstrated which supports approval of FTC/TAF FDC.

(b) (4)

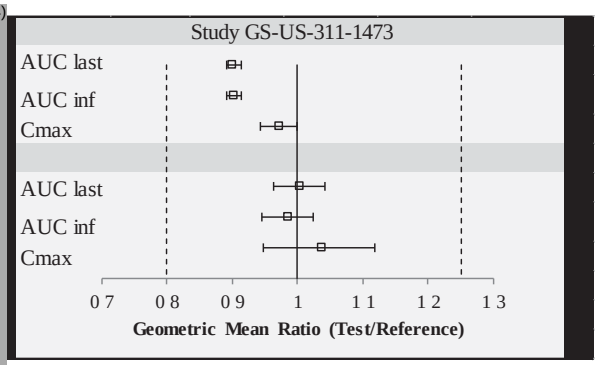

Figure 1. Statistical comparison of FTC/TAF pharmacokinetic parameters. Points represent the ratio of the geometric mean (test/reference) and error bars represent the 90% confidence interval.

The Applicant evaluated the effect of food on the FTC/TAF FDC. Food increases TAF AUC by 77% and does not affect FTC AUC. This effect of food on TAF from FTC/TAF is larger than

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that observed with EVG/COBI/FTC/TAF FDC where TAF AUC increased by 18%. This differential food effect on TAF exposure observed between the two formulations is not likely due to formulation because both products are immediate release formulations with rapid dissolution and manufactured using standard excipients. The Applicant hypothesized that this differential food effect can be attributed to the significant increase in TAF bioavailability (estimated to be ~40% in humans) in the presence of a Pgp inhibitor such as COBI in EVG/COBI/FTC/TAF FDC, thus the presence of food does not lead to a further substantial increase in TAF bioavailability and the relative changes in TAF exposure is low. On the other hand, in the case of FTC/TAF alone, where no Pgp inhibitor is present, the coadministration with food leads to a substantial relative increase in TAF bioavailability.

The clinical pharmacology team agrees with the Applicant's proposal to allow the administration of FTC/TAF FDC without regard to food. The initial concern of the review team was the impact of a 44% reduction in TAF exposure (relative to TAF exposure from EVG/COBI/FTC/TAF FDA) when given under fasted conditions on the efficacy of the various TAF-containing HIV regimens given the unknown TAF exposure-efficacy relationships for these regimens. However, the review team concluded that this reduction in exposure is not expected to have a significant impact on the on the efficacy of the various TAF-containing HIV regimens based on the following:

1. The reduction in TAF exposure in the fasted state relative to the fed state is expected to be ~15% when FTC/TAF is combined with a regimen containing a CYP3A4 inhibitor such as ritonavir or cobicistat because of increased bioavailability due to Pgp inhibition.
2. The lower TAF exposures from FTC/TAF in the fasted state are predicted to maintain antiviral activity based on a TAF monotherapy antiviral activity study.
3. Durability of response is expected to be maintained at lower TAF exposures based on the below observations from a switch study where 292 HIV-1 patients were randomized to continue an FTC/ tenofovir disoproxil fumarate (TDF)-containing regimen or switch to FTC/TAF-containing regimen and regimens were administered without regard to food:
    a. Week 48 virologic success was 93-97% across TAF AUC quartiles. The first quartile exposure range is below the expected exposure of TAF from F/TAF 25 mg under fasted conditions.
    b. TFV-DP concentrations in PBMC (site of action) were higher in the TAF-containing arm relative to the TDF-containing arm regardless of 3rd agent with which FTC/TAF was combined.

The Applicant conducted several drug-drug interaction studies to evaluate the effect of other ARV agents on the exposure of FTC and TAF. Dolutegravir (DTG), efavirenz (EFV), and rilpivirine (RPV) had no clinically significant effect on the exposure of TAF. On the other hand,

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darunavir (DRV)/RTV, lopinavir (LPV)/RTV, atazanavir (ATV)/RTV had variable but significant effects on the PK of TAF (Figure 2).

(b) (4)

Figure 2. Distribution of TAF AUC when administered alone and in the presence of COBI or various HIV-1 protease inhibitors combined with RTV. Figure adapted from clinical pharmacology review. A mean TAF AUC of ~200 ng*h/mL was observed in the EVG/COBI/FTC/TAF pivotal clinical efficacy and safety trials (upper dashed line). A minimum TAF AUC of ~55 ng*h/mL was found to have antiviral activity similar to TDF 300 mg in TAF monotherapy trial (NDA 207561, lower dashed line).

(b) (4)

1. Near-maximal TAF antiviral activity was observed in a monotherapy study at a TAF AUC of ~≥55 ng*h/mL, which is lower than the median AUC observed when FTC/TAF is coadministered with DRV/RTV.

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2. In study GS-US-311-1089 where subjects received FTC/TAF- or FTC/TDF-containing regimens, virologic success of >90% was reported in both treatment arms and TFV-DP concentrations were higher in the FTC/TAF arm regardless of third agent, including PIs. In this study 82 patients were on a DRV/RTV containing regimen.
3. In phase 2 study GS-US-299-0102 where subjects received either DRV/COBI/FTC/TAF [redacted] (b) (4) or DRV/COBI/FTC/TDF, TAF AUCs were lower compared to historical data (mean TAF AUC_{last} of 131 ng*h/mL in this study versus 218 ng*h/mL from EVG/COBI/FTC/TAF clinical efficacy trials). In this study, week 48 virologic outcomes were not statistically different between the treatment arms, and there was no relationship between TAF exposure and virologic outcome.

It should be noted that the team concluded that because the exposure reduction of TAF is greatest with DRV/RTV, compared to ATV/RTV and LPV/RTV, [redacted] (b) (4)

Inspections of the clinical and bioanalytical sites for Study GS-US-311-1473 and Study GS-US-311-1473 were requested. The Office of Study Integrity and Surveillance (OSIS) recommended accepting the bioanalytical and clinical data without an on-site inspection because the bioanalytical site had been inspected recently, relative to the timing of the inspection request, and the nature of identified issues does not warrant another inspection. Please refer to OSIS memorandum dated 06/12/2015 for full details. OSIS also recommended accepting the bioanalytical data and clinical data from Study GS-US-311-1473 following an on-site inspection. Please refer to OSIS memorandum dated 01/05/2016 for full details.

6. Clinical Microbiology

The Applicant did not conduct any new clinical virology studies for this submission. Please refer to the clinical virology review dated 12/02/2015 for full details.

7. Clinical Efficacy and Safety

The NDA is recommended for approval from clinical perspective. The clinical review team recommended [redacted] (b) (4) Please refer to the clinical review dated 12/01/2015 for full details. Also please refer to biometrics review dated 12/18/2015 for detailed review of Study GS-US-299-0102.

The Applicant submitted the efficacy data from Study GS-US-299-0102 which was a phase 2, double-blind, non-inferiority study conducted over years 2012-2014 in treatment-naïve adults

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with HIV-1 infection. A total of 153 subjects were randomly assigned in a 2:1 ratio to one of the following treatments:

[redacted] (b) (4)

2

The primary efficacy endpoint was the percentage of subjects with HIV-1 viral loads < 50 copies/mL using the snapshot algorithm at 24 weeks. The pre-specified non-inferiority margin was 12% on the risk difference scale.

Baseline demographics and disease characteristics were similar between the two treatment arms. Subjects were enrolled in the United States, had a median age of 33 years, were over 90% male, 60% White and 35% Black, and 84% had the risk factor of homosexual sex. Baseline HIV-1 RNA was >100,000 copies/mL in 20% of subjects, CD4 count was < 200 cells/µL in 14% of subjects, and 90% of subjects had asymptomatic infection at baseline.

As shown in Table 1, DRV/COBI/FTC/TAF met the 12% non-inferiority margin for the Week 24 virologic success primary efficacy endpoint. However, DRV/COBI/FTC/TAF did not meet 12% non-inferiority margin at Week 48, which is the FDA recommended endpoint for clinical trials in HIV-1 treatment naïve subjects.

Table 1. Virologic success rates for DRV/COBI/FTC/TAF in GS-US-299-0102. Adapted from biometrics review.

Virologic success	D/C/F/TAF (n = 103)	DRV+COBI+TVD (n = 50)	Difference (95% CI)	P-value
Week 24	77/103 (75%)	37/50 (74%)	3.3% (-11% to 18%)	0.64
Week 48	79/103 (77%)	42/50 (84%)	-6.2% (-20% to 7%)	0.35

The biometrics review team concluded that results of this trial did not provide a statistical basis for concern regarding lack of efficacy for DRV/COBI/FTC/TAF. While numeric trends for the Week 48 endpoint favored the DRV/COBI/FTC/TDF treatment arm, the results were inconclusive and did not approach statistical inferiority.

There were no new safety concerns observed for the FTC/TAF FDC in studies that enrolled healthy subjects (relative bioavailability, food effect, and drug-drug interaction (DDI) studies). There were no deaths and there was a single unrelated Grade 3 serious adverse event (SAE) of

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peritoneal hemorrhage in a subject with sickle cell disease following a dose of FTC/TAF. The following discontinuations were reported in these trials:

1. [redacted] (b) (4)
2. Two subjects in DDI studies discontinued due to Grade 2 anxiety disorder in one case and to Grade 2 joint abscess (unrelated to treatment) in the other.

There were no deaths reported in Study GS-US-299-01027. Seven SAEs were reported: 5 occurring in the DRV/COBI/FTC/TAF arm (allergichypersensitivity, substance abuse, psychosis, cellulitis right lower extremity, bloody Diarrhea) and 2 occurring in the DRV+COBI+FTC/TDF arm (multiple admissions for pneumonia and bronchitis, subacute renal failure possibly due to renal tubular dysfunction.).

Two subjects with SAE in each arm discontinued study drug due to adverse events (AEs) as follows: hypersensitivity/rash and substance abuse in DRV/COBI/FTC/TAF treatment arm and renal tubular dysfunction and chronic diarrhea in DRV/COBI/FTC/TDF treatment arm.
The percentages of patients experiencing an AE, a SAE, a study drug related AE, a discontinuation due to an AE, or Grade 2 or higher AEs were similar between the two treatment arms.

AEs in the eye disorders system organ class (SOC) were reported in 6 (6%) of subjects in the DRV/COBI/FTC/TAF arm compared to none in the DRV/COBI/FTC/TDF arm. One non-SAE of photophobia in the DRV/COBI/FTC/TAF group was assessed as treatment related. These AEs were Grade 1 in severity and did not result in any discontinuation from the trial. No AEs of uveitis noted during the study. All of the 6 SOC eye disorders appear to have a potential inflammatory component. The data provided in this submission does not permit further analysis but the imbalance supports continuing concern.

8. Advisory Committee Meeting

An Advisory Committee meeting was not held for this application.

9. Pediatrics

There are no pediatric data in the application. In the Agreed Initial Pediatric Study Plan submitted on 07/16/2014 for FTC/TAF FDC the Agency agreed with the Applicant on the following:

1. A partial waiver of the requirements to evaluate FTC/TAF FDC in pediatrics < 4 weeks because studies are impossible or highly impracticable. This is due to improvement in

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perinatal transmission prevention strategies resulting in insufficient numbers of neonatal subjects to be enrolled. In addition, even when neonates are identified for enrollment, by the time enrollment is accomplished, dosing is initiated, and drug concentrations have reached steady state, the subjects are likely to be older than 4 weeks of age.

2. Defer the development of FTC/TAF FDC in pediatrics ≥ 4 weeks to < 18 years of age because either pediatric trials with FTC and TAF or development of age appropriate formulation are currently ongoing.

10. Other Relevant Regulatory Issues

Financial disclosures were obtained for the pivotal relative bioavailability study for all of the clinical investigators and were reviewed by this reviewer. All investigators reported having no disclosed financial interests/arrangements and therefore, financial disclosure information does not affect approvability of this application.

At the time of this review, DAVP and the Applicant did not reach a mutual agreement regarding the dosage strength of FTC/TAF (200/25 mg (b) (4) that should be recommended for co-administration with PIs combined with CYP3A inhibitor such as COBI or RTV. The following scenarios are under considerations:

(b) (4)

2. Recommend FTC/TAF 200/25 mg dosage strength for co-administration with DRV or LPV or ATV when combined with COBI or RTV. This recommendation will ensure the attainment of TAF exposure that is at least similar, if not higher, than that observed with EVG/COBI/FTC/TAF FDC. The corresponding increase in TFV exposure is expected to be significantly lower than that observed with TDF 300 mg, albeit it will be higher than that observed with EVG/COBI/FTC/TAF FDC. This increase in TAF exposure is not expected to compromise safety.
3. Recommend FTC/TAF 200/25 mg dosage strength for co-administration with DRV or LPV when combined with COBI or RTV (b) (4) This proposal takes into account the relatively lower decrease in TAF exposure (relative to that from EVG/COBI/FTC/TAF, ~21%) when FTC/TAF is co-administered with ATV/RTV or ATV/COBI as opposed to that observed with DRV or LPV combined with CYP3A inhibitor. Administration of FTC/TAF 200/25 mg with ATV/RTV or ATV/COBI is expected to produce TAF exposure that is 2 fold higher than that obtained from EVG/COBI/FTC/TAF FDC. TFV exposure is expected to be increased to levels similar to those observed with DRV/RTV.

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This increase is not expected to compromise safety. This proposal provides a pathway to compensate for lower TAF exposure expected with DRV or LPV (which can be administered without regard to food leading for further decrease in TAF exposure) and does not lead to higher TAF exposures expected when FTC/TAF 200/25 mg is co-administered with ATV/RTV or ATV/COBI.

11. Labeling

The proposed proprietary name DESCOVEY for FTC/TAF FDC was considered acceptable. Please refer Office of Medication Error Prevention and Risk Management memorandum dated 05/15/2015 for full details.

Review and discussions with the Applicant regarding of the contents of this product prescribing information (PI) are ongoing at the time of this review. DAVP recommended that the summary of essential safety and efficacy information for use of FTC/TAF FDC should be contained directly in the PI to meet the requirements of 21CFR 201.56(a)(1). DAVP recommended minimizing the reference to GENVOYA® PI because it may be confusing to healthcare providers to refer to different PIs and it may not be clear to healthcare providers what aspects of the other PI to review. DAVP also requested the Applicant to make the PI compliant with Pregnancy and Lactation Labeling Rule.

12. Recommendations/Risk Benefit Assessment

12.1 Recommended Regulatory Action: Approval

12.2 Risk Benefit Assessment: The risk-benefit profile of FTC/TAF FDC is acceptable based on the assessment of the review team. Because FTC/TAF FDC combination produced similar exposure to EVG/COBI/FTC/TAF FDC the risks and benefits of the FTC/TAF FDC is considered similar to those FTC/TAF in EVG/COBI/FTC/TAF FDC. Efficacy and safety of FTC and TAF were established previously in clinical trial in HIV-1 patients.

12.3 Recommendation for Postmarketing Risk Evaluation and Management Strategies: None

12.4 Recommendation for other Postmarketing Requirements and Commitments: A PMR will be issued for pediatric studies under the Pediatric Research Equity Act (PREA) and consistent with the Agreed Initial Pediatric Study Plan.

12.5 Recommended Comments to Applicant: None

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/s/

ISLAM R YOUNIS
02/25/2016

Cross-Discipline Team Leader Review Addendum

NDA	208215
Submission Type	505(b)(1)
Applicant	Gilead Sciences, Inc.
Submission Date	04/07/2015
Generic Name	Emtricitabine (FTC)/Tenofovir alafenamide (TAF)
Trade Name	DESCOVEY
Dosage Form (Strength)	[redacted] (b) (4) FDC Tablet (FTC 200 mg / TAF 25 mg)
Proposed Indication	Treatment of HIV-1 infection in adults and pediatrics patients 12 years of age and older.
CDTL	Islam R. Younis, Ph.D.
Recommendation	Approval

At the time of finalization of the CDTL review for this NDA, DAVP and the Applicant did not reach a mutual agreement regarding the dosage strength of FTC/TAF (200/25 [redacted] (b) (4) that should be recommended for co-administration with the protease inhibitors (PIs) (darunavir (DRV), lopinavir (LPV), and atazanavir (ATV)) combined with CYP3A inhibitor such as cobicistat (COBI) or ritonavir (RTV).

DAVP recommends FTC/TAF (200/25 mg) to be co-administered with PIs combined with a CYP3A4 inhibitor because this dosage strength is expected to produce plasma TAF exposures similar to or greater than TAF exposures from EVG/COBI/FTC/TAF, the reference product used to approve FTC/TAF (Table 1). DAVP decided to target systemic plasma TAF exposures rather than intracellular levels of TFV diphosphate (TFV-DP, the active moiety) because TFV-DP concentrations in peripheral blood mononuclear cells may not be representative of TFV-DP concentrations in other relevant tissues, associated with EVG/COBI/FTC/TAF efficacy. This conservative approach aims to ensure maximal efficacy of FTC/TAF PI-based HIV regimens given the concerns with the numerical decrease in virologic success at Week 48 observed in Study GS-US-299-0102 (recognizing the limitations of this trial) which can potentially be attributed to reduced TAF exposures. [redacted] (b) (4) (b) (4)

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Table 1. Observed and Predicted TAF and TFV mean AUC for TAF in Combination with Protease Inhibitors and CYP3A Inhibitor.

Source	TAF Dose (mg)	TAF		TFV		
		AUC (ng*h/mL)	AUC Ratio relative to Genvoya	AUC (ng*h/mL)	AUC Ratio relative to Genvoya	AUC Ratio relative to Stribild
Stribild*				4400		1.00
Genvoya*	10	210	1.0	290	1.0	0.07
ATV/RTV+TAF	(b) (4)					
	25**	408	1.9	255	0.9	0.06
LPV/RTV+TAF	(b) (4)					
	25**	303	1.4	333	1.1	0.08
DRV/RTV+TAF	(b) (4)					
DRV/COBI+TAF	25	239	1.1	935	3.2	0.21

* Phase 3 data
** Predicted Exposures

The following points were taken into consideration for the three PIs:

1. FTC/TAF (200/25 mg) when combined with DRV/RTV or DRV/COBI will produce similar plasma TAF exposures to that observed from EVG/COBI/FTC/TAF. The corresponding increase in TFV exposures relative to FTC/TAF (200/10 mg) is not expected to compromise the safety of the regimen because this exposure is 5 times lower than TFV exposure observed with EVG/COBI/FTC/TDF.

2. FTC/TAF (200/25 mg) when combined with LPV/RTV or LPV/COBI will produce plasma TAF exposures slightly higher than that observed from EVG/COBI/FTC/TAF. The expected increase in TAF exposures and the expected corresponding increase in TFV exposures are not expected to compromise the safety of the regimens. Note that LPV/RTV or LPV/COBI can be taken under fasted conditions which can lead to further decreases in TAF exposures and produce TAF exposures that are comparable to that from EVG/COBI/FTC/TAF due to the differential food effect on FTC/TAF compared to EVG/COBI/FTC/TAF.

3. ATV/RTV or ATV/COBI will produce plasma TAF exposures that exceed those observed when combined with DRV or LPV plus CYP3A inhibitor and are lower than those

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observed with EVG/COBI/FTC/TAF. TAF exposures resulting from ATV/CYP3A inhibitor plus FTC/TAF (200/25 mg) are not expected to compromise the safety of this regimen. Also, recommending one FTC/TAF dosage strength to be administered with all antiretroviral agents will provide a less confusing dosing recommendation for health care providers.

In conclusion, FTC/TAF (200/25 mg) is the best available option at this point that will not compromise the efficacy of PI+CYP3A inhibitor + FTC/TAF regimens without significantly increasing safety risks. The Applicants agreed to DAVP recommendation.

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ISLAM R YOUNIS
04/04/2016